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A dynamic design space for primary drying during batch freeze-drying

KEYWORDS: Dynamic Design Space, freeze-drying, mathematic modeling.

Abstract Biopharmaceutical products are emerging within the pharmaceutical industry. However, biopharmaceuticals are often unstable in aqueous solution. Freeze-drying (lyophilisation) is the preferred method to achieve a stable product with an increased shelf-life. During batch freeze-drying, there are only two adaptable process variables, i.e. the shelf temperature and the pressure in the drying chamber. The value of both should be optimized, preferably in a dynamic way, to minimise the primary drying time while respecting process and equipment constraints and ensuring end product quality. A mechanistic model is used to determine the optimal values for the adaptable variables, hereby accounting for the uncertainty in all involved model parameters. A dynamic Design Space was constructed with a risk of failure acceptance level of 0.01%, i.e. a 'zero-failure' situation. Even for a risk of failure of 0.01%, the computed settings resulted in a reduction of the drying time by over 50% compared to current practice.

INTRODUCTION

Among the approved biopharmaceutical drug products, approximately 50% are freeze-dried products (1). This indicates that freeze-drying or lyophilisation is the method of preference to stabilise biopharmaceuticals which are unstable in an aqueous solution. However, freeze-drying has some major drawbacks as it is an expensive, time- and energy-consuming process (2, 3). As common in the pharmaceutical sector, freeze-drying is a batch process, consisting of three major process steps: (a) a freezing step where vials filled with the aqueous drug formulation are placed on temperature-controlled shelves which are gradually cooled until approximately -45°C, leading to crystallization of most of the water into ice, (b) a primary drying step under vacuum conditions (approximately 10 Pa), during which the shelves provide the energy required for ice removal by sublimation, and (c) a secondary drying step, where the remaining unfrozen water is removed by desorption until a dry cake is obtained (Figure 1). To ensure end product quality, several Critical Quality Attributes (CQAs) are defined for freeze-dried products (4,5). To guarantee optimal therapeutic activity, the Active Pharmaceutical Ingredient (API) should stay stable throughout the lyophilisation process. Additionally, the residual moisture content of the dried cake needs to be at an adequate level to ensure product stability. During primary drying, the temperature at the

sublimation front is critical and should always remain below the collapse temperature to avoid cake collapse and maintain a proper cake structure, another important CQA (5). According to current best practices, fixed values for the adaptable process variables, shelf temperature and chamber pressure, are used during the process. This conservative approach leads to suboptimal freeze-drying cycles with long processing times. Optimisation of the freeze-drying process (i.e., reducing process time) requires the temperature at the sublimation front to be as high as possible (6). In this contribution, the most optimal conditions for the primary drying step are strived for. Therefore, a mechanistic model has been used to optimise the dynamic values of shelf temperature and chamber pressure, ensuring that the product temperature is kept under the critical value (7-8). Due to the continuous change of model input parameters with the progress of primary drying, e.g. the dry product mass transfer resistance increases with the increase of the dried layer thickness or the vial heat transfer coefficient, the optimal combination of the adaptable process parameters is dynamic rather than static. The mechanistic primary drying model, relying on the underlying physical mechanisms and the fundamental understanding of the process under study, allows the determination of the dynamic Design Space. The Design Space is defined in ICH Q8 as the multidimensional combination and interaction of input variables and process parameters

leading to the expected product specifications with a controlled (i.e., high) probability. By taking the uncertainty on the model parameters into account, the risk of collapse can be quantitatively estimated for a specific combination of shelf temperature and chamber pressure to minimise and control the risk of failure.

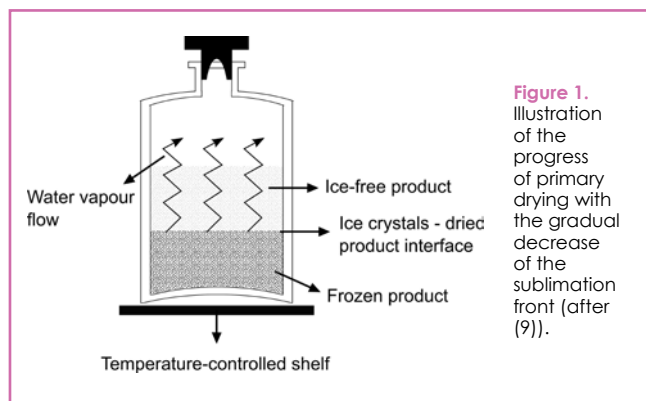


Figure 1. Illustration of the progress of primary drying with the gradual decrease of the sublimation front (after (9)).

MODELLING THE PRIMARY DRYING STEP

The mechanistic primary drying model consists of two stages: (a) the chamber pressure is first decreased exponentially from ambient pressure to vacuum till the sublimation rate becomes positive; and, (b) the second phase where the thickness of the dried layer gradually increases as the sublimation process proceeds. The mathematical model is based on the basic principles of mass and energy transfer. During the first phase, the shelf temperature is fixed at the final freezing temperature and the temperature at the sublimation front equals the shelf temperature. During the second phase, a set of equations is solved simultaneously to calculate the temperature at the sublimation front and the temperature difference across the ice layer (10). An important aspect during sublimation is the dry product mass transfer resistance, which depends on the used formulation and the microstructure of the dry layer (pore size). Moreover, the dry product mass transfer resistance changes in function of the dried layer thickness, which is determined experimentally. The evolution of the length of the dried layer in function of time for optimal values of shelf temperature and chamber pressure is presented in figure 2. The steep decrease of the chamber pressure at the start is obvious. During this initial steep decrease the sublimation rate is zero, and therefore, the thickness of the dried layer is zero. After an increase of the shelf temperature at the beginning of the sublimation, it decreases again till a value around 18°C.

THE CONCEPT OF DYNAMIC DESIGN SPACE

The use of the term 'Design Space' is only justified when the uncertainty on the model parameters is taken into account. The uncertainty on the parameters is considered here by performing a large number of simulations for different combinations of the parameter values. Therefore, for each parameter an uncertainty level is set, and by performing a Sobol sampling a large number of combinations for the parameters

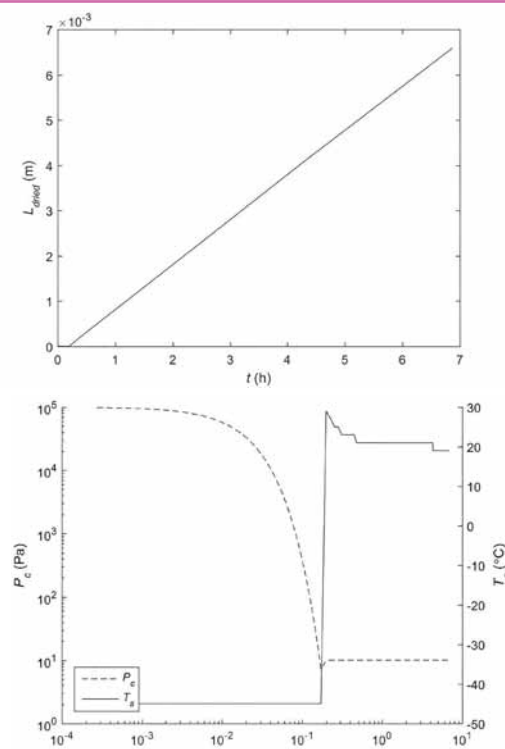
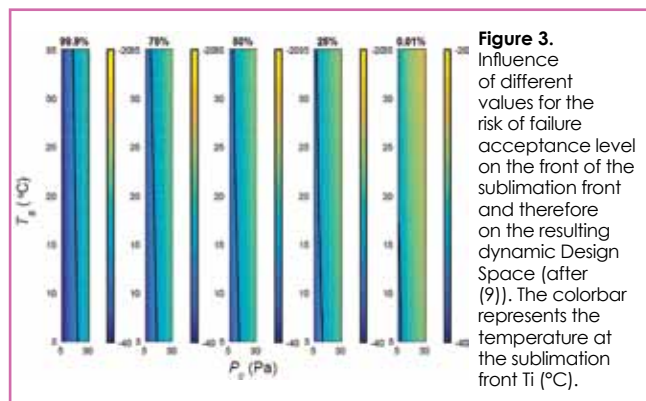


Figure 2. Evolution of the thickness of the dried layer (Left) for optimal values of shelf temperature (T_s) and chamber pressure (P_c) (Right) in function of time (after (9)).

are generated. For each parameter combination the output is calculated using the model (9). Only in this case, the risk of failure is under control, as the risk of exceeding the critical temperature at the sublimation front is known because the uncertainty on the parameters involved in the model is taken in to account. The optimal combination of the shelf temperature and chamber pressure can be determined for several values of the risk of failure acceptance level (Figure 3-4). The influence of the risk of failure acceptance level on the Design Space is obvious (Figure 3). The more conservative the risk of failure is chosen, the smaller the Design Space is, i.e. there will be less combinations of the shelf temperature and the chamber pressure where the critical temperature at the sublimation front is not exceeded with a certain level of confidence (the combinations on the left of the black lines in Figure 3).

As the risk of failure acceptance level decreases, the shelf temperature and the chamber pressure have to be set at a lower value (Figure 4). As a consequence the sublimation rate will be lower and the freeze-drying process will take longer. Experiments were performed to test the different risk of failure levels. Only the experimental cycle with a risk of failure acceptance level of 0.01% yielded good cakes. The other four experimental cycles performed using the calculated process settings with a higher risk of failure acceptance level produced cakes with signs of collapse, which is totally unacceptable. Moreover, the experimentally observed degree of collapse increased with the increase of the risk of failure. Therefore, to ensure the product quality it is necessary to take the uncertainty



on the model parameters into account. The computed primary drying time of a conservative cycle with shelf temperature and chamber pressure fixed at -20°C and 10 Pa respectively, was 19.5h. Even if the risk of failure equals 0.01%, the processing time is decreased with more than 50% in comparison with this suboptimal cycle with fixed settings, as is current practice.

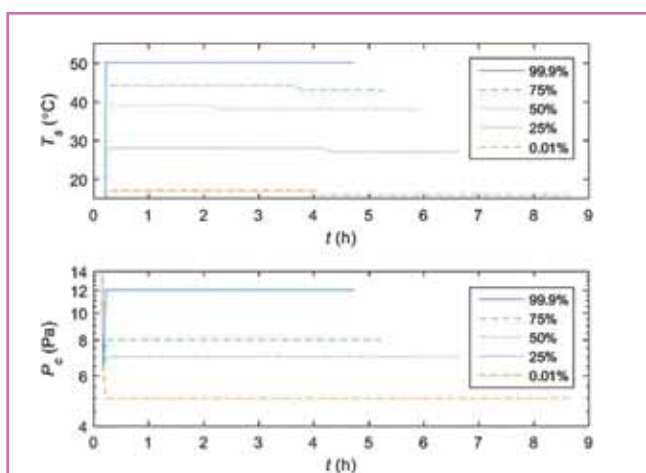


Figure 4. The evolution of the shelf temperature (T_s) and the chamber pressure (P_c) in function of time for several values of the risk of failure acceptance level (after (9)).

DISCUSSION

By using a mechanistic model to determine the optimal values for the process variables during primary drying, the processing time can be significantly reduced. Before the model predictions can be used to draw conclusions on a Design Space, the validity and reliability of the model should be verified. Experimental data collection is therefore needed. Currently, applying fixed values for the process variables is common practice with suboptimal process conditions as a consequence. Therefore, due to the low value for the shelf temperature – a conservative choice to guarantee product quality – the processing time is high. The inclusion of the uncertainty on the model parameters is needed to minimise the risk of failure, given the limitation of knowledge currently embedded in the fairly simple model. However, the used uncertainty level on the model parameters will influence the results, and therefore it is important to select a realistic

uncertainty level. By decreasing the uncertainty level of the parameters, the optimal values for the shelf temperature and the chamber pressure will be closer to the values which are obtained without taking the uncertainty into account (Figure 2). Another future route is to put more rigour and knowledge into the model, hereby reducing the uncertainty and allowing to operate the system at even more optimal conditions. However, in the meantime a significant reduction in processing time can already be achieved with confidence.

CONCLUSION

By using a fairly simple dynamic mathematical model for the primary drying step of a freeze-drying process, the optimal dynamic combination of the shelf temperature and the chamber pressure has been determined. This allowed finding more optimal dynamic operational conditions that reduce the processing time by over 50%, even for a risk of failure acceptance level of 0.01%. By accounting for the uncertainty on the model parameters the risk of failure was controlled. Experimental data collection revealed that only a risk of failure acceptance level of 0.01% yielded good cakes, i.e. the structure of the produced freeze-dried product was not lost. Therefore, it can be concluded that an uncertainty analysis is an essential part for the determination of the dynamic Design Space based on mechanistic models that always have a certain degree of uncertainty. Further reducing the uncertainty will allow to further optimize the system.

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